C1 increased efficacy of the immunotoxin, the carboxyl-terminal endoplasmic reticulum retrieval signal Lys-Asp-Glu-Leu was added to the sequence of gelonin. A person having ordinary skill in this art would readily recognize that certain modifications in the sequence of scFv-23 could be made, e.g., a V_H - Linker - V_L format and CDR grafting to construct a humanized or chimeric antibody to minimize potential immunogenicity problems with this murine antibody.--

REMARKS

Claims 15-19 remain in this application.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

The 35 U.S.C. §112 Rejections

Claim 18 remains rejected under 35 U.S.C. §112, first paragraph, as not enabled. This rejection is respectfully traversed.

The Examiner has rejected claim 18 because the specification fails to show that the cell line producing scFv-23 is known and readily available to the public or has been deposited by the inventor. A deposit of the 23-3825 plasmid encoding the scFv-23 single chain antibody was made with the American Type Culture Collection under the conditions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure on December 21, 2000. Applicants submit herewith a true copy of the Deposit Receipt and a Declaration of Deposit for the 23-3825 plasmid. The specification has been amended herein to include a reference to the deposited 23-3825 plasmid encoding the scFv-23 single chain antibody. The Applicants respectfully request that the 35 U.S.C. §112, first paragraph rejection of claim 18 be withdrawn.

The 35 USC §103 Rejections

Claims 15 and 19 stand rejected under 35 USC §103(a) as unpatentable over **Bacus** (U.S. Patent No. 5,514,554) in view of **Rosenblum** (*Cancer Communication*, 1991) and **Hudziak** (*Molecular and Cellular Biology*, 1989). This rejection is respectfully traversed.

Bacus teaches ricin conjugated to an anti-c-erbB antibody via SPCP crosslinking. **Rosenblum** describes the conjugation of tumor necrosis factor to monoclonal antibody against a melanoma cell specific 240 kDa glycoprotein, an entirely different antigen than that of the instant invention. **Hudziak** reports that unconjugated monoclonal antibody against $p185^{HER2}$/anti-erbB2 sensitizes breast cancer cells to unconjugated tumor necrosis factor.

The instant invention improves on **Hudziak** by administering TNF concurrently with the sensitizing antibody. While this was more effective and specific than separate administration of each entity, one skilled in the art still could not determine from the combination of **Bacus, Rosenblum** and **Hudziak** whether tumor necrosis factor conjugated to an anti-$p185^{HER2}$/anti-erbB2 antibody would be effective against the target cells. It is possible that

the conjugation event might disrupt the domains of the TNF moiety essential to its function. Alternatively, the binding site of the antibody might be blocked in the conjugate eliminating the specific targeting of the resulting conjugate. Time-consuming, non-routine experimentation, beyond that which is obvious to one skilled in the art, would be required to determine if the anti-p185^{HER2}/anti-erbB2-TNF conjugate would exhibit the same effect as the separate administration of each component. Therefore, the Applicants respectfully request that the 35 USC §103(a) rejection of claims 15 and 19 as obvious over **Bacus** in view of **Rosenblum** and **Hudziak** be withdrawn.

Claims 15, 16, 17 and 19 stand rejected under 35 USC §103(a) as unpatentable over **Wels** *et al.* (US Patent No. 5,571,894) in view of **Hoogenboom** *et al.* (*Biochimica et Biophysica Acta*, 4:345-354, 1991) and **Hudziak** *et al.* (*Molecular and Cellular Biology*, 1989). This rejection is respectfully traversed.

Wels *et al.* teaches the fusion of an anti-c-erbB2 single chain antibody to an effector such as a toxin or drug but does not teach conjugation to tumor necrosis factor. **Hoogenboom** *et al.*

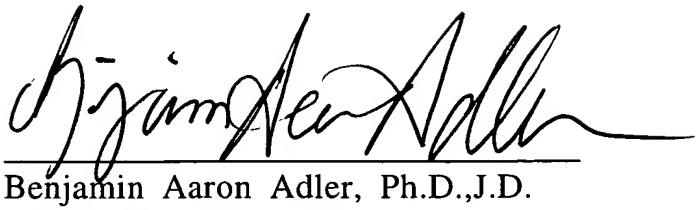
teaches a single chain antibody-TNF fusion protein but this fusion protein binds to a different antigen that that of the instant invention. **Hudziak** teaches that a monoclonal antibody against $p185^{HER2}$/anti-erbB2 sensitizes breast cancer cells to tumor necrosis factor but does not teach the conjugation of the monoclonal antibody to tumor necrosis factor. No combination of the above references indicates whether a conjugate of an anti-$p185^{HER2}$/anti-erbB2 antibody and tumor necrosis factor would be still be effective against the target cells. It is possible that the conjugation event might disrupt the domains of the TNF moiety essential to its function or block the binding site of the antibody. Time-consuming, non-routine experimentation, beyond that which is obvious to one skilled in the art, would be required to determine if the anti-$p185^{HER2}$/anti-erbB2-TNF conjugate was effective. Accordingly, the Applicants respectfully request that the rejection of claims 15, 16, 17 and 19 under 35 USC §103(a) as obvious over **Wels** in view of **Hoogenboom** and **Hudziak** be withdrawn.

This is intended to be a complete response to the Office Action mailed December 22, 2000. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned

attorney of record for immediate resolution.

Respectfully submitted,

DATE: June 14, 2001



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning on page 70, line 17 has been amended as follows:

Figure 8 shows a schematic of the construction of the scFv23-gelonin immunotoxin gene. A single-chain analogue of the antibody e-23 was raised against an epitope on the 185 kD antigen p185HER-2/neu found on the surface of breast and ovarian carcinomas. The 12 amino acid 212 linker was chosen to tether the two variable regions of the antibody since this sequence was shown to provide for proteolytic stability and functional antibody in several instances. The resulting scfv-23 single chain antibody is encoded by plasmid 23-3825 and is available as ATCC Patent Deposit Designation PTA-2845. Alternately other linker sequences such as the flexible Gly-rich peptide, linking peptides from multidomain proteins, or other designed peptides e.g. the 202, 202', 205, and 218 could have been selected. In addition a functional linker could have been selected from a randomized sequence library using phage display technology or

a colony filter-lift hapten-binding assay. Furthermore, short linker sequences used in the construction of diabodies could also have been chosen. Antibodies recognizing tumor cell-surface epitopes have the ability to selectively localize within human tumors after systemic administration and therefore can serve as targeting probes for the site-specific delivery of cytotoxic chemotherapeutic agents such as Pseudomonas exotoxin, ricin or gelonin. An immunotoxin was constructed with sFv-23 and gelonin. In addition, with a view to increased efficacy of the immunotoxin, the carboxyl-terminal endoplasmic reticulum retrieval signal Lys-Asp-Glu-Leu was added to the sequence of gelonin. A person having ordinary skill in this art would readily recognize that certain modifications in the sequence of scFv-23 could be made, e.g., a V_H - Linker - V_L format and CDR grafting to construct a humanized or chimeric antibody to minimize potential immunogenicity problems with this murine antibody.